Comparison of human papillomavirus genotypes, sexual, and reproductive risk factors of cervical adenocarcinoma and squamous cell carcinoma: Northeastern United States

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OBJECTIVE: Although human papillomavirus causes essentially all cervical carcinoma, cofactors may differ by cancer histologic type. We examined human papillomavirus genotypes and sexual and reproductive risk factors for cervical adenocarcinoma and squamous cell carcinoma.

STUDY DESIGN: One hundred twenty-four women with adenocarcinoma, 139 women with squamous cell carcinoma, and 307 control subjects participated in this case-control study. Logistic regression analyses were performed to calculate odds ratios and CIs.

RESULTS: Human papillomavirus 18 was associated most strongly with adenocarcinoma (odds ratio, 105; 95% CI, 23-487). Human papillomavirus 16 was associated most strongly with squamous cell carcinoma (odds ratio, 30; 95% CI, 12-77). More than three lifetime sexual partners was a risk factor for adenocarcinoma (odds ratio, 2.1; 95% CI, 1.1-4.0) and squamous cell carcinoma (odds ratio, 3.0; 95% CI, 1.6-5.9). Even being pregnant was associated inversely with adenocarcinoma (odds ratio, 0.4; 95% CI, 0.2-0.8). Five or more pregnancies was associated with squamous cell carcinoma (odds ratio, 2.2; 95% CI, 0.9-5.4).

CONCLUSION: The relative importance of human papillomavirus genotypes 16 and 18 and the reproductive co-factor differences suggest distinct causes for cervical adenocarcinoma and squamous cell carcinoma.
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Key words: Cervical carcinoma, human papillomavirus, cervical adenocarcinoma, reproductive history

Although adenocarcinomas of the cervix comprise a minority of all cervical cancers that are diagnosed in the United States and elsewhere, approximately 20% of cervical cancers are adenocarcinomas. The rates of the more common squamous cell tumors of the cervix have been declining in many countries, although adenocarcinoma rates have not. In fact, some evidence exists to suggest that rates of cervical adenocarcinoma are increasing in some populations because of changes in detection or real changes in disease occurrence over time.[1] Human papillomavirus infection (HPV) is a necessary factor for these two histologic types of cervical cancer.[2] Approximately one half of cervical squamous cell carcinomas are attributed to HPV genotype 16 infection,[2] and approximately one half of cervical adenocarcinomas are attributed to HPV genotype 18.[3]

The recognition that HPV infection causes virtually all cervical cancer calls for careful classification of HPV status of cases and control subjects in the study of other cofactors for these cancers.[4] Only a few large epidemiologic studies of cervical adenocarcinoma have attempted to collect HPV DNA from either cases or control subjects.[5,6] These and other studies suggest that the cofactors that contribute to the progression of HPV to cervical adenocarcinoma are distinct from those for squamous cell carcinoma.[7-9] Smoking and parity, for example, appear to increase the risk of squamous cell carcinoma but protect against adenocarcinoma.[10-13]

To elucidate cofactors for adenocarcinoma, we conducted a multicenter case-controlled study of cervical adenocarcinoma, squamous cell carcinoma, and community-based control subjects. We previously reported differences between histologic types with respect to smoking,[12]

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Table I. Number of women with cervicovaginal specimens and total number of women enrolled by case-control group

Cervicovaginal swab	*Control subjects*	*Adenocarcinoma*	*Squamous cell carcinoma*	*All women*
Collected	255 (83%)	116 (94%)	129 (93%)	500 (88%)
Not collected	52 (17%)	8 (6%)	10 (7%)	70 (12%)
All women	307 (100%)	124 (100%)	139 (100%)	570 (100%)

oral contraceptives,[14] and hormone replacement therapy.[15] In this study we evaluated HPV status, sexual and reproductive risk factors for cervical adenocarcinoma, and squamous cell carcinoma.

Material and methods

The study enrolled 124 women who were between 18 to 69 years old who had cervical carcinoma that demonstrated glandular differentiation. Eighty-six women had a histologic diagnosis of adenocarcinoma (31 women with carcinoma in situ and 55 women with invasive neoplasms), 25 women had adenosquamous carcinoma (2 women with carcinoma in situ and 23 women with invasive neoplasms), and 13 women with rare glandular tumors, all of which were invasive neoplasms (henceforth referred to as adenocarcinoma cases). Cases were ascertained retrospectively between January 1992 and June 1994 and were ascertained prospectively between July 1994 and March 1996. Three pathologists reviewed the reports and histologic specimens of 109 adenocarcinoma cases to confirm the diagnoses. Institutional review board clearance was obtained from the National Cancer Institute and six clinical centers in the northeastern United States.

To evaluate whether risk factors differ by cancer histologic type, we enrolled 139 cases with squamous cell cervical carcinomas, which were matched to adenocarcinoma cases at a 1:1 ratio on clinic, age at diagnosis (±5 years), to diagnosis date (±3 months), and stage of disease at diagnosis (in situ versus invasive carcinoma). Forty-eight cases had carcinoma in situ, and 91 cases had invasive squamous cell carcinomas. Matching criteria were relaxed when a squamous cell carcinoma case could not be matched to an index adenocarcinoma case.

Control subjects were identified by random digit dialing of households in telephone exchange of each adenocarcinoma case. Adult women were enumerated by age and ethnicity. The response rate was 79%. Potential control subjects, who were matched on age (±5 years), ethnicity, and telephone exchange were called to determine hysterectomy status, with a response rate of 75%. Hysterectomy-free control subjects were matched individually 2:1 to adenocarcinoma cases. Matching criteria were relaxed when a control could not be matched to an index adenocarcinoma case.

Cervicovaginal cells were collected for HPV DNA testing from participants with the use of both self-administered and clinician-administered Dacron swabs. Some cervical cancer cases had been treated for their disease before cervicovaginal specimens could be collected. The principal treatment was partial or complete removal of the cervix. Women with pretreatment specimens had cervicovaginal swabs that were collected from both the endocervix and ectocervix. Swabs that were collected after treatment were taken from the vaginal cuff. Control subjects were invited to visit the clinic from which their index case was recruited to complete data collection. Participants had an option of in-home interview and specimen collection. Only self-administered specimens were collected in-home. There was 88% agreement of positivity and negativity for self-administered and clinician collected swabs.[16] A polymerase chain reaction–based reverse line blot detection system (MY09/11 L1 consensus primer system) discriminated 27 HPV genotypes.[16] Other primers were used to rule out media contamination with a plasmid that contained a segment of HPV 16 DNA.[14] Specimens were grouped hierarchically by HPV genotype: 18, 16, 18-related (39, 45, 59, and 68), other oncogenic (26, 31, 33, 35, 51, 52, 55, 56, and 58), and low-risk (6, 11, 40, 42, 51, 53, 54, 57, 66, 73, 82, 83, and 84).

Participants completed interviews with trained staff. To avoid the collection of information on exposures that occurred after diagnosis and to exclude Papanicolaou screening that led to diagnosis, cases reported exposures before a reference date of 12 months before diagnosis. Control subjects were assigned the reference date of their index adenocarcinoma case. Participants were asked about the number of lifetime sexual partners, partners during the 10 years after first intercourse, and in the 5 most recent years. They were also asked about their age at first intercourse and condom use. Questions about reproductive factors included age at menarche, number of pregnancies, number of live births, vaginal and caesarean deliveries, and age at first pregnancy.

Of 203 potential adenocarcinoma cases, 18 cases were diagnosed with rare forms of cervical carcinomas of nonglandular differentiation and were therefore ineligible for study. Among the remaining 185 cases, 11 cases could not be located, 10 cases could not be enrolled for other reasons, 7 cases died before enrollment, 27 cases declined to participate, 2 cases were too ill, and 4 cases were never interviewed, for a response rate of 124 of 185 cases (67%). Of 255 potential cases of squamous cell carcinoma, 14 cases were found not to be eligible.

Table II. HPV genotypes of cases and control subjects and associations with cancer histologic type for all cases with cervicovaginal specimens and with pretreatment specimens

		Adenocarcinoma			*Squamous cell carcinoma*		
*HPV DNA status**	*Control subjects (No.)*	*No.*	*OR†*	*95% CI†*	*No.*	*OR†*	*95% CI†*
All cases with specimens							
HPV 18	4	12	11.9	3.6-39.5	6	5.2	1.4-19.4
HPV 16	14	19	5.3	2.4-11.4	38	10.5	5.2-21.2
HPV 18-related types	7	4	2.3	0.6-8.4	5	2.9	0.9-9.6
Other oncogenic types	11	3	1.1	0.3-4.1	8	3.0	1.1-8.1
Low-risk types	13	20	6.1	2.8-13.4	13	4.3	1.8-10.2
HPV positive	49	58	4.7	2.9-7.8	70	5.8	3.5-9.4
HPV negative	206	58	1.0	Referent	59	1.0	Referent
Total	255	116			129		
Cases with pretreatment specimens							
HPV 18	4	10	105.2	22.7-487.1	5	19.6	4.6-83.8
HPV 16	14	14	47.6	14.1-161.2	22	30.5	12.1-76.8
HPV 18-related types	7	1	6.1	0.6-62.0	1	2.7	0.3-25.3
Other oncogenic types	11	0	—	—	4	8.6	2.2-33.3
Low-risk types	13	2	7.0	1.1-42.6	1	1.6	0.2-14.3
HPV positive	49	27	24.1	9.0-64.6	33	14.6	6.7-31.8
HPV negative	206	6	1.0	Referent	12	1.0	Referent
Total	255	33			45		

*Hierarchical order: HPV 18, HPV 16, HPV 18-related types (HPV 39, 45, 59, 68), other oncogenic types (HPV 26, 31, 33, 35, 51, 52, 56, 58, 82), low-risk types (HPV 6, 11, 40, 42, 53, 54, 55, 57, 66, 73, 83, 84).

†Age-adjusted: 22 squamous cell carcinoma cases and 9 adenocarcinoma cases did not have information on the time of sample collection that was relative to treatment, including 11 squamous cell carcinoma cases and 3 adenocarcinoma cases whose test results were positive for HPV.

Among the remaining 241, 29 cases could not be located, 25 cases died before enrollment, 7 cases were never interviewed, 38 cases declined to participate, and 3 cases were too ill, for an overall response rate of 139 of 241 cases (58%). Of 470 potential community-based control subjects, 15 subjects could not be located, 21 subjects were ineligible for other reasons, 126 subjects declined to participate, and 1 subject was too ill to participate, for an overall response rate of 307 of 470 subjects (65%). The final study population comprised 124 adenocarcinoma cases, of whom 116 cases (94%) provided cervicovaginal specimens, 139 squamous cell carcinoma cases including 129 women (93%) who provided specimens, and 307 control subjects of whom 255 women (83%) provided specimens.

Unconditional logistic regression was used to calculate the odds ratios (ORs) and 95% CIs to avoid loss of cases without matched control subjects and because control subjects were individually matched to adenocarcinoma cases, but not to squamous cell carcinoma cases. Regression models were adjusted for age (<30, 30-39, 40-49, 50-59, ≥ 60 years), household income (<$30,000 vs ≥$30,000), and confounding variables that altered parameter estimates for dependent variables by 10% or more: HPV status (negative, nononcogenic, oncogenic, missing); lifetime sexual partners (<4 versus ≥4), ever versus never pregnant, and Papanicolaou tests in the past 10 years (<10 vs ≥10). Confounding by HPV was addressed by including HPV status in logistic regression models and by comparing HPV-positive control subjects to all cases. Variables that changed parameter estimates by <10% were dropped (eg, smoking, age at first intercourse, clinic, and ethnicity). To assess whether exposures differed by case group, adjusted polytomous regression analyses were performed.[17] SAS version 8.0 (SAS Institute Inc, Cary, NC) was used to compute analyses.

Results

As previously reported, the median age of women with adenocarcinoma was 38 years (range, 21-67 years), with similar distributions for age-matched squamous cell carcinoma cases and control subjects.[14] Although 90% of cases with adenocarcinoma were white and 6% were African American, 81% of cases with squamous cell carcinoma were white and 13% were African American, and 86% of control subjects were white and 9% were African American. Sixty-three percent of adenocarcinoma cases reported postsecondary education compared with 42% of squamous cell carcinoma cases and 65% of control subjects. Annual household income of ≥$30,000 was reported by 65% of adenocarcinoma cases, 52% of squamous cell carcinoma cases, and 73% of control subjects. In the 10 years before the reference date, 58% of adenocarcinoma cases reported annual Papanicolaou tests compared with 42% of squamous cell carcinoma cases and 49% of control subjects.

HPV detection and genotyping. Cervicovaginal specimens were obtained from 500 of 570 women (88%) in

Table III. Distributions and associations with sexual behaviors and condom use by cervical cancer histology

	*All women enrolled in study**							*HPV-positive control group**				
		Adenocarcinoma			*Squamous cell carcinoma*				*Adenocarcinoma*		*Squamous cell carcinoma*	
Sexual history	*Control subjects (No.)*	*No.*	*OR†*	*95% CI†*	*No.*	*OR†*	*95% CI†*	*Control subjects (No.)*	*OR‡*	*95% CI‡*	*OR‡*	*95% CI‡*
Lifetime partners												
1	96	24	1.0	Referent	19	1.0	Referent	10	1.0	Referent	1.0	Referent
2-3	77	21	1.1	0.5-2.2	29	1.9	0.9-4.0	9	0.6	0.2-2.0	1.8	0.5-6.1
4+	125	76	2.1	1.1-4.0	90	3.0	1.6-5.9	29	1.1	0.4-3.1	1.8	0.6-4.9
Partners in 10 years after first intercourse												
1	125	33	1.0	Referent	37	1.0	Referent	14	1.0	Referent	1.0	Referent
2-3	69	35	2.5	1.3-4.9	43	2.9	1.6-5.6	5	2.7	0.8-9.3	4.5	1.3-16
4+	104	55	2.1	1.1-4.1	57	1.8	1.0-3.4	29	1.0	0.4-2.7	1.2	0.5-3.2
Partners in previous 5 years												
1	121	58	1.0	Referent	63	1.0	Referent	12	1.0	Referent	1.0	Referent
2+	69	34	0.8	0.4-1.6	44	1.0	0.5-1.8	24	0.4	0.1-0.9	0.4	0.2-1.0
Age at first intercourse												
>20 y	92	34	1.0	Referent	21	1.0	Referent	11	1.0	Referent	1.0	Referent
17-19 y	125	52	0.9	0.5-1.8	65	1.9	1.0-3.6	15	1.5	0.5-4.6	2.4	0.8-7.1
< 17 y	90	38	0.9	0.5-1.8	53	2.0	1.0-3.9	23	0.8	0.3-2.4	1.5	0.5-4.3
Duration of condom use												
Never	73	39	1.0	Referent	49	1.0	Referent	10	1.0	Referent	1.0	Referent
< 1 y	61	21	0.6	0.3-1.3	31	0.6	0.3-1.3	9	0.6	0.2-2.0	0.6	0.2-1.8
1-4 y	81	29	0.6	0.3-1.1	22	0.3	0.2-0.7	16	0.5	0.2-1.6	0.4	0.1-1.1
>4 y	80	27	0.6	0.3-1.2	28	0.5	0.3-1.0	13	0.6	0.2-1.7	0.5	0.2-1.4

*Excludes missing responses.
†Adjusted for age, income, frequency of Papanicolaou tests, HPV DNA status (negative, nononcogenic types, oncogenic types, missing data), and pregnancy. Models for age of first intercourse and condom use were also adjusted for the number of sexual partners.
‡Adjusted as above except that HPV DNA status was dropped from model.

the study population (Table I). HPV genotypes were determined for all 177 HPV-positive participants: 58 adenocarcinoma cases, 70 squamous cell carcinoma cases, and 49 control subjects (Table II). HPV DNA was detected in a higher proportion of cases with pretreatment cervicovaginal specimens than cases with pretreatment and posttreatment specimens combined: 27 of 33 cases (82%) versus 58 of 116 cases (50%) for adenocarcinoma cases and 33 of 45 cases(73%) versus 70 of 129 cases (54%) for squamous cell carcinoma cases. Among cases with specimens that were collected before treatment, HPV 16, which accounted for 14 cases of adenocarcinoma (42%) was the most common genotype in the hierarchical analyses as presented in Table II. HPV 18, which accounted for 10 cases of adenocarcinoma (30%) and 5 cases of squamous cell carcinoma (11%), was the next most common genotype for both case groups. In analyses that were restricted to cases with pretreatment specimens, HPV 18 was associated strongly with adenocarcinoma (OR, 105; 95% CI, 23-487), and HPV 16 was associated most strongly with squamous cell carcinoma (OR, 30; 95% CI, 12-77). Multiple HPV types were detected in 17 HPV-positive control subjects (35%), 15 adenocarcinoma cases (26%), and 20 squamous cell carcinoma cases (29%). In 31 of the 52 women (60%) with multiple HPV types detected, 2 HPV types were detected; for the remaining 21 women, ≥3 types were observed.

Sexual history. In analyses that included all control subjects, ORs for both histologic types of cervical cancer increased with number of lifetime sexual partners (Table III). Compared with women who reported one partner, women with cervical adenocarcinoma were twice as likely (OR, 2.1; 95% CI, 1.1-4.0) and women with squamous cell carcinoma were three times as likely (OR, 3.0; 95% CI, 1.6-5.9) to report ≥4 partners. Compared with women who reported one partner in the 10 years after first intercourse, women with adenocarcinoma were more than twice as likely (OR, 2.5; 95% CI, 1.3-4.9) and women with squamous cell carcinoma were three times as likely (OR, 2.9; 95% CI, 1.6-5.6) to report two or three partners during this time. Four or more partners during the 10 years after first intercourse was also associated with adenocarcinoma (OR, 2.1; 95% CI, 1.1-4.1) and squamous cell carcinoma (OR, 1.8; 95% CI, 1.0-3.4). A similar proportion of

Table IV. Distribution and associations with reproductive factors by cervical cancer histologic type

		All women enrolled in study							*HPV-positive control group*			
		Adenocarcinoma			*Squamous cell carcinoma*				*Adenocarcinoma*		*Squamous cell carcinoma*	
Reproductive factors	*Control subjects (No.)*	*No.*	*OR**	*95% CI*	*No.*	*OR**	*95% CI*	*Control subjects (No.)*	*OR†*	*95% CI*	*OR†*	*95% CI*
Age at menarche												
>13 y	151	55	1.0	Referent	61	1.0	Referent	19	1.0	Referent	1.0	Referent
12 y	98	36	0.9	0.5-1.5	40	1.1	0.6-1.8	21	0.4	0.2-0.9	0.5	0.2-1.2
< 12 y	56	31	1.4	0.8-2.7	34	2.0	1.1-3.7	9	1.4	0.3-2.7	1.6	0.6-4.3
Ever pregnant												
No	52	30	1.0	Referent	19	1.0	Referent	10	1.0	Referent	1.0	Referent
Yes	255	94	0.4	0.2-0.8	120	1.1	0.6-2.2	39	0.5	0.2-1.2	1.0	0.4-2.6
Pregnancies												
0	52	30	1.0	Referent	19	1.0	Referent	10	1.0	Referent	1.0	Referent
1-2	119	42	0.4	0.2-0.8	51	1.1	0.5-2.3	18	0.5	0.2-1.3	0.9	0.3-2.6
3-4	102	37	0.4	0.2-0.9	39	0.9	0.4-1.8	17	0.4	0.2-1.3	1.8	0.3-2.3
≥5	34	15	0.4	0.2-1.1	30	2.2	0.9-5.4	4	0.7	0.1-3.0	3.1	0.7-14
Live births												
0	77	46	1.0	Referent	32	1.0	Referent	17	1.0	Referent	1.0	Referent
1-2	163	49	0.5	0.3-0.8	63	1.0	0.5-1.7	22	0.5	0.2-1.2	1.0	0.4-2.4
≥3	67	29	0.6	0.3-1.3	44	1.7	0.8-3.4	10	0.5	0.2-1.7	1.8	0.6-5.3
Cesarean delivery‡												
No	178	65	1.0	Referent	88	1.0	Referent	25	1.0	Referent	1.0	Referent
Yes	52	13	0.7	0.3-1.4	19	0.7	0.4-1.5	7	0.8	0.2-2.7	0.9	0.3-2.6
Age of first pregnancy§												
≥26 y	79	19	1.0	Referent	17	1.0	Referent	7	1.0	Referent	1.0	Referent
20-25 y	113	44	1.3	0.6-2.6	54	1.8	0.9-3.6	21	0.8	0.2-2.8	1.1	0.4-3.7
20 y	62	28	1.7	0.7-4.0	47	2.6	1.2-5.8	11	1.9	0.4-8.4	1.6	0.4-6.3
Age of first birth§												
≥26 y	88	23	1.0	Referent	22	1.0	Referent	9	1.0	Referent	1.0	Referent
20-25 y	102	40	1.0	0.5-2.0	47	1.6	0.8-3.2	17	0.7	0.2-2.3	1.2	0.4-3.9
<20 y	40	15	1.4	0.5-3.6	38	3.2	1.4-7.7	6	1.3	0.3-6.2	2.9	0.6-13

Data excludes missing responses.
*Adjusted for age, income, frequency of Papanicolaou tests, HPV status (negative, nononcogenic types, oncogenic types, missing data), and number of sexual partners. Age of menarche also adjusted for pregnancy.
†Adjusted for age, income, frequency of Papanicolaou tests, and number of sexual partners. Age of menarche also adjusted for pregnancy.
‡Restricted to parous women.
§Restricted to women who reported pregnancy and adjusted for the number of pregnancies.

cases and control subjects reported one partner in the previous 5 years.

Early age at first intercourse (<17 years vs referent group [≥20 years]) was associated with squamous cell carcinoma (OR, 2.0; 95% CI, 1.0-3.9) but not with adenocarcinoma (OR, 0.9; 95% CI, 0.5-1.8). Compared with no reported condom use, ever use was associated inversely for both histologic types of cancer (ORs between 0.3 and 0.6). No duration response effect was evident for condom use.

In analyses that were restricted to HPV-positive control subjects and all cases, point estimates of the associations between number of lifetime partners, partners in the 10 years after first intercourse, and age of first intercourse remained greater than the null for squamous cell carcinoma (Table III). Residual associations for adenocarcinoma were less evident; however, an association with two or three partners in the 10 years after first intercourse remained. A higher proportion of HPV-positive control subjects reported ≥2 partners during the previous 5 years than either adenocarcinoma (OR, 0.4; 95% CI, 0.1-0.9) or squamous cell carcinoma cases (OR, 0.4; 95% CI, 0.2-1.0). Inverse associations between condom use and both cancer histologic types were of similar magnitude.

Reproductive history. Menarche before age 12 years was associated with squamous cell carcinoma (OR, 2.0; 95% CI, 1.1-3.7; Table IV). Ever pregnant was associated inversely with adenocarcinoma (OR, 0.4; 95% CI, 0.2-0.8), and ≥5 pregnancies was associated with squamous cell carcinoma (OR, 2.2; 95% CI, 0.9-5.4). Nonsignificant inverse associations were seen between ever versus never having had caesarean delivery and both histologic types. The association between age at first pregnancy (<20 vs >25 years of age, referent group) was slightly stronger for squamous cell carcinoma (OR, 2.6; 95% CI, 1.2-5.8) than for adenocarcinoma (OR, 1.7; 95% CI, 0.7-4.0) and persisted for squamous cell carcinoma after stratification by

number of pregnancies (data not shown). The association between age at first birth was also stronger for squamous cell carcinoma (OR, 3.2; 95% CI, 1.4-7.7) than for adenocarcinoma (OR, 1.4; 95% CI, 0.5-3.6).

In analyses that were restricted to HPV-positive control subjects and all cases, associations differed by cancer histologic type for ever versus never pregnant, ≥5 pregnancies, and number of live births (Table IV).

Case group comparisons. Fully adjusted polytomous regression analyses that compared adenocarcinoma and squamous cell carcinoma cases with control subjects produced results that were similar to those for unconditional logistic regression analyses presented in Tables III and IV. Differences in associations by cancer histologic type emerged for two key reproductive risk factors: ever versus never pregnant ($P = .06$) and the number of pregnancies (<5 vs ≥5; $P = .04$).

Comment

In this report, adenocarcinomas and squamous cell carcinomas shared HPV and many sexual behaviors as risk factors but had different reproductive risk factors. The principal findings of this study were the inverse association between gravidity and cervical adenocarcinoma and the positive association between high gravidity and cervical squamous cell carcinoma. Previous analyses from this case-controlled study have suggested other differences in cofactors by histologic type. Smoking was associated with squamous cell carcinomas and was associated inversely with adenocarcinomas[12]; current oral contraceptive use was associated only with adenocarcinoma in situ,[14] and hormone replacement therapy was associated with adenocarcinoma but not squamous cell carcinoma.[15] Taken together, these findings suggest that many of the cofactors that influence cervical adenocarcinoma[5,6,7,13] are similar to those seen for endometrial adenocarcinoma. On the basis, in part, of associations with smoking, obesity, and reproductive cofactors, endometrial adenocarcinoma is postulated to have an underlying hormonal cause[18] in which the opposing effects of estrogen and progesterone on tissue proliferation have a critical role.[19] Although our study did not address these hormonal factors directly, the findings suggest that reproductive events, presumably related to hormones, have different effects on the progression of HPV infection to cervical cancer according to histologic type.

Consistent with a previous report,[3] HPV genotype 18 infections were associated most strongly with adenocarcinoma. Conversely, HPV genotype 16 was associated most strongly with squamous cell carcinoma. Although the biologic basis for associations between HPV genotypes and cancer histologic type are unknown, it is noteworthy that hormones are reported to affect HPV genotype 16 and 18 gene expression differently.[20]

Because HPV is a common infection and a necessary cause of virtually all cervical cancer,[2] we addressed HPV status in several ways to evaluate sexual and reproductive cofactors of cervical cancer.[4] After the restriction of the analyses to the HPV-positive control strata, associations between two sexual risk factors (lifetime sexual partners and age of first intercourse) remained stronger for squamous cell carcinoma than for adenocarcinoma. Two possible explanations for these observations are residual confounding that is related to HPV infection[4] and etiologic differences between the two histologic types of cervical cancer, with squamous cell carcinoma having a greater venereal component (other than HPV) than adenocarcinoma.[21] Inverse associations with condom use may also reflect the role of sexually transmitted factors in both histologic types of cancer.[5]

The current study provides the strongest evidence to date of an association between nulliparity and cervical adenocarcinoma and supports the findings from a pooled analysis of International Agency for Research on Cancer studies that show a stronger association between number of pregnancies and squamous cell carcinoma than adenocarcinoma.[11] As in other studies, early age at first pregnancy and age at first birth were associated with increased risk of squamous cell carcinoma.[11,22] Similar, although weaker, effects were also suggested for adenocarcinoma. The effect of young age at first pregnancy has been postulated to relate to the susceptibility of young adult women to HPV infection, to ectopy, or to other age-related factors.[23] Although the association between age of first pregnancy and squamous cell carcinoma was not explained by the number of pregnancies in this study, in a larger study of pooled data from eight International Agency for Research on Cancer case-control studies, the association with age of first pregnancy did lose statistical significance after an adjustment was made for the number of term pregnancies.[11]

Strengths and weaknesses of our study deserve mention. The lack of pretreatment cervical specimens from all cases reduced the number of cases with reliable HPV genotype data. Direct analysis of surgical specimens might have yielded additional HPV genotype data than the collection of cervicovaginal swabs; however, more than three fourtsh of the cases with pretreatment swabs tested positive for HPV DNA. Although our HPV-positive control stratum was small, analyses that were restricted to this group supported the principal findings of the main analysis. Squamous cell carcinoma cases were matched to adenocarcinoma cases and therefore were not representative of squamous cell carcinoma cases in the population. Bias because of nonresponse was possible if distributions of HPV genotypes, sexual, and reproductive risk factors differed for eligible adenocarcinoma cases, squamous cell carcinoma cases, and control subjects who did not participate. Validation studies suggest that the self-reporting of women's sexual[24] and reproductive his-

tories[25] are unlikely to cause misclassification of these exposures. Recall bias is unlikely to explain the opposite direction of associations between reproductive history and cancer histologic type, unless the bias operates at the histologic level rather than at the level of cancer site. The review of histologic specimens from nearly all adenocarcinoma cases by pathologists reduced the possibility that endometrial adenocarcinomas were misclassified as cervical adenocarcinomas.

In summary, in this study, reproductive cofactors differed by cervical cancer histologic type. Although both types of cervical cancer are caused by HPV infection, some of the reproductive risk factors for cervical adenocarcinoma parallel those for endometrial adenocarcinoma, which suggests that hormonal risk factors may differ for cervical adenocarcinoma and squamous cell carcinoma. Future studies may explain the underlying mechanisms for the observed differences in cofactors by cervical cancer histologic type.

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REFERENCES

1. Vizcaino AP, Moreno V, Bosch FX, Munoz N, Barros-Dios XM, Parkin DM. International trends in the incidence of cervical cancer, I: adenocarcinoma and adenosquamous cell carcinomas. Int J Cancer 1998;75:536-45.
2. Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 2002;55:244-65.
3. Andersson S, Rylander E, Larsson B, Strand A, Silfversvard C, Wilander E. The role of human papillomavirus in cervical adenocarcinoma carcinogenesis. Eur J Cancer 2001;37:246-50.
4. Franco EL. The sexually transmitted disease model for cervical cancer: incoherent epidemiologic findings and the role of misclassification of human papillomavirus infection. Epidemiology 1991;2:98-106.
5. Ursin G, Pike MC, Preston-Martin S, d'Ablaing G III, Peters RK. Sexual, reproductive, and other risk factors for adenocarcinoma of the cervix: results from a population-based case-control study (California, United States). Cancer Causes Control 1996;7:391-401.
6. Madeleine MM, Daling JR, Schwartz SM, Shera K, McKnight B, Carter JJ, et al. Human papillomavirus and long-term oral contraceptive use increase the risk of adenocarcinoma in situ of the cervix. Cancer Epidemiol Biomarkers Prev 2001;10:171-7.
7. Parazzini F, La Vecchia C, Negri E, Fasoli M, Cecchetti G. Risk factors for adenocarcinoma of the cervix: a case-control study. Br J Cancer 1988;57:201-4.
8. Brinton LA, Tashima KT, Lehman HF, Levine RS, Mallin K, Savitz DA, et al. Epidemiology of cervical cancer by cell type. Cancer Res 1987;47:1706-11.
9. Brinton LA, Herrero R, Reeves WC, de Britton RC, Gaitan E, Tenorio F. Risk factors for cervical cancer by histology. Gynecol Oncol 1993;51:301-6.
10. Hildesheim A, Herrero R, Castle PE, Wacholder S, Bratti MC, Sherman ME, et al. HPV co-factors related to the development of cervical cancer: results from a population-based study in Costa Rica. Br J Cancer 2001;84:1219-26.
11. Munoz N, Franceschi S, Bosetti C, Moreno V, Herrero R, Smith JS, et al. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. Lancet 2002;359:1093-101.
12. Lacey JV Jr, Frisch M, Brinton LA, Abbas FM, Barnes WA, Gravitt PE, et al. Associations between smoking and adenocarcinomas and squamous cell carcinomas of the uterine cervix (United States). Cancer Causes Control 2001;12:153-61.
13. Korhonen MO. Epidemiological differences between adenocarcinoma and squamous cell carcinoma of the uterine cervix. Gynecol Oncol 1980;10:312-7.
14. Lacey JV Jr, Brinton LA, Abbas FM, Barnes WA, Gravitt PE, Greenberg MD, et al. Oral contraceptives as risk factors for cervical adenocarcinomas and squamous cell carcinomas. Cancer Epidemiol Biomarkers Prev 1999;8:1079-85.
15. Lacey JV Jr, Brinton LA, Barnes WA, Gravitt PE, Greenberg MD, Hadjimichael OC, et al. Use of hormone replacement therapy and adenocarcinomas and squamous cell carcinomas of the uterine cervix. Gynecol Oncol 2000;77:149-54.
16. Gravitt PE, Peyton CL, Apple RJ, Wheeler CM. Genotyping of 27 human papillomavirus types by using L1 consensus PCR products by a single-hybridization, reverse line blot detection method. J Clin Microbiol 1998;36:3020-7.
17. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley; 1989.
18. Parazzini F, La Vecchia C, Negri E, Fedele L, Balotta F. Reproductive factors and risk of endometrial cancer. Am J Obstet Gynecol 1991;164:522-7.
19. Hale GE, Hughes CL, Cline JM. Endometrial cancer: hormonal factors, the perimenopausal "window of risk," and isoflavones. J Clin Endocrinol Metab 2002;87:3-15.
20. Chen YH, Huang LH, Chen TM. Differential effects of progestins and estrogens on long control regions of human papillomavirus types 16 and 18. Biochem Biophys Res Commun 1996;224:651-9.
21. Smith JS, Munoz N, Herrero R, Eluf-Neto J, Ngelangel C, Franceschi S, et al. Evidence for *Chlamydia trachomatis* as a human papillomavirus cofactor in the etiology of invasive cervical cancer in Brazil and the Philippines. J Infect Dis 2002;185:324-31.
22. Bosch FX, Munoz N, de Sanjose S, Izarzugaza I, Gili M, Viladiu P, et al. Risk factors for cervical cancer in Colombia and Spain. Int J Cancer 1992;52:750-8.
23. Critchlow CW, Wolner-Hanssen P, Eschenbach DA, Kiviat NB, Koutsky LA, Stevens CE, et al. Determinants of cervical ectopia and of cervicitis: age, oral contraception, specific cervical infection, smoking, and douching. Am J Obstet Gynecol 1995; 173:534-43.
24. Jeannin A, Konings E, Dubois-Arber F, Landert C, Van Melle G. Validity and reliability in reporting sexual partners and condom use in a Swiss population survey. Eur J Epidemiol 1998;14:139-46.
25. Bosetti C, Tavani A, Negri E, Trichopoulos D, La Vecchia C. Reliability of data on medical conditions, menstrual and reproductive history provided by hospital controls. J Clin Epidemiol 2001;54:902-6.